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Essential Role for Programmed Cell Death of Adult Produced Dentate Gyrus Neurons in Synaptic Plasticity and Hippocampus-Dependent Behaviors

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In the dentate gyrus (DG) of adult hippocampus, a considerable number of new neurons are generated daily, but only a subset of these survive as a majority of adult-generated neurons undergo programmed cell death (PCD). The functional role of neuronal generation and death in the normal physiology of the adult brain, however, remain to be elucidated. Several markers for apoptosis failed to reveal cell death in Bax-deficient mice, and this, together with a progressive increase in neuron number in the DG of the Bax knock-out, indicates that Bax is critical for the PCD of adult-generated hippocampal neurons. Whereas the proliferation of neural progenitor cells was not altered in the Bax-knock-out, there was an accumulation of doublecortin, calretinin+, and NeuN+ postmitotic neurons, suggesting that Bax-mediated PCD of adult-generated neurons takes place during an early phase of differentiation. To assess the role of PCD in the adult brain, the electrophysiological and behavioral characteristics of adult Bax-KO mice were examined. Electrophysiological examination revealed that the efficacy of DG→CA3 synaptic transmission was selectively reduced and mossy fiber LTP was absent in adult (6-month) Bax-KO mice. The morphology of mossy fibers (MF) in Bax-KO suggests increased competition among excess MFs for contacts with a limited number of CA3 spines, which would alter synaptic properties. Coincident with these impairments, Bax-KO mice exhibited reduced performance in contextual fear memory tasks. These results suggestthat PCD in the adult brain is required for functional efficacy of the DG→CA3 circuitry involved in the maintenance of efficient associative memory processes.